

# Modeling Charge-Sign Asymmetric Solvation Free Energies With Nonlinear Boundary Conditions

Jaydeep P. Bardhan<sup>1</sup> and Matthew G. Knepley<sup>2</sup>

<sup>1</sup>*Dept. of Electrical and Computer Engineering, Northeastern University, Boston MA 02115*

<sup>2</sup>*Computation Institute, The University of Chicago, Chicago IL 60637*

We show that charge-sign-dependent asymmetric hydration can be modeled accurately using linear Poisson theory but replacing the standard electric-displacement boundary condition with a simple nonlinear boundary condition. Using a single multiplicative scaling factor to determine atomic radii from molecular dynamics Lennard-Jones parameters, the new model accurately reproduces MD free-energy calculations of hydration asymmetries for (i) monatomic ions, (ii) titratable amino acids in both their protonated and unprotonated states, and (iii) the Mobley “bracelet” and “rod” test problems [J. Phys. Chem. B, v. 112:2408, 2008]. Remarkably, the model also justifies the use of linear response expressions for charging free energies. Our boundary-element method implementation demonstrates the ease with which other continuum-electrostatic solvers can be extended to include asymmetry.

## I. INTRODUCTION

Implicit-solvent models represent an intuitive and fast approach to understand molecular solvation<sup>1?–3</sup>, and have a rigorous statistical-mechanical interpretation as an approximation to the potential of mean force (PMF) experienced by a molecular solute due to the surrounding solvent molecules<sup>1</sup>. The PMF is usually decomposed into non-polar and electrostatic terms, the latter of which are often modeled using macroscopic continuum models based on the Poisson–Boltzmann partial-differential equation (PDE). Continuum models approximate the free energy required to grow the solute charge distribution into the solute cavity<sup>1,4?–10</sup>. Although implicit-solvent models can be orders of magnitude faster than explicit-solvent molecular-dynamics (MD) simulations, most popular continuum theories ignore numerous potentially important effects, including solvent molecules’ finite size and specific molecular interactions such as hydrogen bonding (the AGBNP2 model, which addresses the latter, is a notable exception<sup>7</sup>).

One of the Poisson model’s most perplexing and long-standing shortcomings is the difficulty of extending it to model charge-sign asymmetric solvation: for example, given two monatomic ions of equal radius, one of  $+q$  charge and the other of  $-q$ , the negative charge experiences stronger interactions with the solvent (more negative solvation free energy)<sup>5,11–17</sup>. However, standard Poisson models are charge-sign *symmetric*; that is, they predict the same solvation free energy for  $\pm q$ . The need to include asymmetric effects is difficult to exaggerate, particularly in biological contexts. Consider that the protein avidin binds its ligand biotin with a binding free energy of approximately  $-20$  kcal/mol, one of the most favorable in biology<sup>18</sup>; solvent-exposed  $+1e$  and  $-1e$  charges can experience as much as 40 kcal/mol difference in their solvation free energies<sup>17</sup>. Dominant factors in charge-sign asymmetric response include the liquid-vapor interface potential<sup>12,14</sup> and the fact that water hydrogens can approach a negative solute charge closer

than water oxygens can approach a positive one<sup>5,11,16,17</sup>. Spherical solutes with central charges provide a useful data set for developing an understanding of size- and charge-sign dependent hydration, including the characterization of interface potentials, solvent packing, and dielectric saturation<sup>11,12,14,15,19,20</sup>. These analyses and the continuum macroscopic-dielectric framework suggest that improvements require a more detailed, accurate representation of the solvent dipole field  $\mathbf{P}(\mathbf{r})$ <sup>21,22</sup>, or, equivalently, the solvent charge density  $\rho_{\text{induced}}(\mathbf{r}) = \nabla \cdot \mathbf{P}(\mathbf{r})$ . Because  $\mathbf{P}$  and  $\rho_{\text{induced}}$  do *not* respond linearly to the solute charge distribution<sup>23</sup>, particularly in the first solvent shell<sup>24</sup>, many groups have developed solvent models in which the solvent potential obeys a nonlinear partial differential equation (PDE)<sup>25–29</sup>. Unfortunately, most of these models are still charge-sign symmetric.

However, in 1939 Latimer et al. proposed an approach to increase or decrease an ion’s radius based on the charge<sup>5</sup>, and recent developments in high-performance computing and explicit-solvent MD free-energy calculations provide important new data to extend this approach. Mobley et al. constructed a challenging test set and conducted extensive MD simulations on charge-sign asymmetry<sup>30</sup>, enabling important new developments in modeling asymmetry<sup>24,31,32</sup> that extend Latimer’s work to Generalized-Born (GB) models of complex solutes. GB theory was a natural setting for these developments because Latimer’s work and GB theory share the conceptual picture of an effective atomic radius. These early studies provided an important insight: a buried charge still affects the electric field at the boundary, so merely parameterizing charge-dependent radii cannot (indeed, should not) provide a satisfactory explanation. The accuracy of asymmetric GB models suggests that a simple Poisson-based model exists, but finding one has proven to be surprisingly difficult.

In this paper, we propose a simple Poisson continuum model that includes charge-sign asymmetry and show that it is remarkably accurate even without parameterization on an atom-by-atom basis. The key feature of

our theory is a *nonlinear boundary condition* (NLBC) for the normal displacement field; in contrast, the displacement boundary condition for the standard (symmetric) Poisson theory is linear<sup>33</sup>. Importantly, even though our proposed displacement boundary condition is nonlinear, the electrostatic potential in the solvent and solute volumes still satisfy *linear* Poisson/Laplace equations. Two phenomena motivated us to propose a nonlinear boundary condition instead of a nonlinear governing equation. First, numerous results illustrate that the solute reaction potential obeys nearly linear response even though the solvent charge distribution does not<sup>17,24,31,32,34,35</sup>. For example, the new asymmetric Generalized-Born (GB) models use the charge distribution only to modify the Born radii, with the overall energy still computed using superposition (independent sum of individual charge responses)<sup>24,31,32</sup>. Furthermore, we found in our previous work that the solute reaction potential is essentially a *piecewise-linear* function of charge<sup>17</sup>, i.e. the proportionality coefficient depends on whether one is charging an ion from zero to  $+q$  or to  $-q$ . In fact, we began this work seeking primarily to reproduce this curiously simple nonlinearity.

The second phenomenon motivating our NLBC approach is the fact that the solute reaction potential is a harmonic field—that is, it satisfies the Laplace equation. This property is useful for numerical computations<sup>36,37</sup> and also provides a path to improve models via boundary-integral methods<sup>38</sup>: harmonicity means that regardless of the solvent model of interest, there exists *some* surface charge density that reproduces the reaction potential inside. For a given solvent model, the surface charge density might satisfy a nonlinear boundary-integral equation, but the very fact that such a density always exists suggests that one might improve continuum models by adding nonlinear terms to widely used BIE formalisms<sup>39–42</sup>.

## II. CONTINUUM MODEL AND EXTENSION TO NONLINEAR BOUNDARY CONDITIONS

We first present the standard (charge-sign symmetric) Poisson electrostatic model and then describe the difference between it and our proposed NLBC model. In both theories, the molecular solute is treated as a macroscopic linear dielectric continuum obeying the Poisson equation  $\nabla^2 \varphi_1(\mathbf{r}) = -\frac{\rho(\mathbf{r})}{\epsilon_1}$  where  $\mathbf{r}$  is a point in space,  $\varphi_1(\mathbf{r})$  is the potential in the solute,  $\epsilon_1$  is the relative permittivity, and the molecular charge distribution  $\rho(\mathbf{r})$  is a set of  $N_q$  point charges, i.e.  $\rho(\mathbf{r}) = \sum_{i=1}^{N_q} q_i \delta(\mathbf{r} - \mathbf{r}_i)$ . The solute and solvent are separated by the interface  $\Gamma$ , and the solvent exterior is a linear dielectric with permittivity  $\epsilon_2 \gg \epsilon_1$ , so the electric potential obeys  $\nabla^2 \varphi_2(\mathbf{r}) = 0$ ; note that modeling realistic biological solutions requires inclusion of screening effects due to mobile ions using e.g. some form of the Poisson-Boltzmann equation for  $\varphi_2(\mathbf{r})$ <sup>2,3</sup>. From macroscopic dielectric theory and Gauss's

law, we obtain the standard Maxwell boundary conditions for  $\mathbf{r}_\Gamma \in \Gamma$

$$\varphi_1(\mathbf{r}_\Gamma) = \varphi_2(\mathbf{r}_\Gamma), \quad (1)$$

$$\epsilon_1 \frac{\partial \varphi_1}{\partial n}(\mathbf{r}_\Gamma) = \epsilon_2 \frac{\partial \varphi_2}{\partial n}(\mathbf{r}_\Gamma), \quad (2)$$

where  $\frac{\partial}{\partial n}$  denotes the normal derivative (the normal at  $\mathbf{r}_\Gamma$  is defined pointing outward into solvent). Assuming that  $\varphi_2(\mathbf{r})$  decays sufficiently quickly as  $|\mathbf{r}| \rightarrow \infty$ , this mixed-dielectric Poisson problem is well posed and the unknown potential  $\varphi_1$  can be rewritten as a linear boundary-integral equation for an unknown surface charge distribution on  $\Gamma$ . In particular, the apparent-surface charge (ASC) model<sup>40,42,43</sup> (also known as the polarizable continuum model<sup>3,44</sup>) can be interpreted as finding an equivalent surface charge  $\sigma(\mathbf{r})$  in a homogeneous medium with permittivity  $\epsilon_1$  everywhere. In this equivalent problem, the analogous boundary condition to Eq. 2 is simpler due to homogeneity, but adds a term for the surface charge:

$$\frac{\sigma(\mathbf{r}_\Gamma)}{\epsilon_1} = \frac{\partial \hat{\varphi}_1}{\partial n}(\mathbf{r}_\Gamma) - \frac{\partial \hat{\varphi}_2}{\partial n}(\mathbf{r}_\Gamma), \quad (3)$$

and we use  $\hat{\varphi}_i = \varphi_i$  to emphasize our use of an equivalent problem. Defining  $G(\mathbf{r}; \mathbf{r}') = \frac{1}{4\pi\|\mathbf{r} - \mathbf{r}'\|}$ , one obtains

$$\left( I + \hat{\epsilon} \left( -\frac{1}{2} I + K \right) \right) \sigma = -\hat{\epsilon} \sum_i^{N_q} q_i \frac{\partial G}{\partial n} \quad (4)$$

where  $\hat{\epsilon} = (\epsilon_2 - \epsilon_1)/\epsilon_2$  and  $K$  is the normal electric field operator<sup>42</sup>. The reaction potential in the solute is then  $\varphi^{REAC}(\mathbf{r}) = \frac{1}{\epsilon_1} \int_\Gamma G(\mathbf{r}; \mathbf{r}') \sigma(\mathbf{r}') dA'$ , and  $\varphi_1(\mathbf{r}) = \varphi^{REAC}(\mathbf{r}) + \varphi^{Coulomb}(\mathbf{r})$ , with the latter term representing the Coulomb potential due to  $\rho(\mathbf{r})$ .

The standard Maxwell displacement boundary condition Eq. 2 is obtained using Gauss's law in integral form and the fact that the divergence of the polarization field  $\mathbf{P}(\mathbf{r})$  represents a volume charge density. However, near the solute-solvent boundary, the assumption that  $\mathbf{P}(\mathbf{r})$  is pointwise proportional to the local electric field breaks down due to water structure at the interface; that is, it is no longer necessarily true that  $\mathbf{P}(\mathbf{r}) = (\epsilon(\mathbf{r}) - 1)\mathbf{E}(\mathbf{r})$ .

To model nonlinear solvent response at the boundary, we propose to replace the linear boundary condition, Eq. 2, with the phenomenological nonlinear boundary condition

$$f(E_n) \frac{\partial \varphi_1}{\partial n}(\mathbf{r}_\Gamma) = (1 + f(E_n)) \frac{\partial \varphi_2}{\partial n}(\mathbf{r}_\Gamma) \quad (5)$$

where  $E_n$  is the electric field just inside  $\Gamma$ , i.e.  $E_n = -\sum_i q_i \frac{\partial G}{\partial n} - K\sigma$ , and

$$f(E_n) = \frac{\epsilon_1}{\epsilon_2 - \epsilon_1} - h(E_n); \quad (6)$$

$$h(E_n) = \alpha \tanh(\beta E_n - \gamma) + \mu. \quad (7)$$

with  $\alpha$ ,  $\beta$ , and  $\gamma$  representing model parameters and  $\mu = -\alpha \tanh(-\gamma)$ . The specification of  $\mu$  ensures that  $h(E_n = 0) = 0$ , so that in the limit of weak electric fields, such as induced at the surface by a deeply buried charge, the boundary condition reduces to the familiar Poisson model. The NLBC leads to the modified, *nonlinear* BIE

$$\left( I + \hat{\epsilon} \left( -\frac{1}{2} I + K \right) + h(E_n) \right) \sigma = -\hat{\epsilon} \sum_i q_i \frac{\partial G}{\partial n}, \quad (8)$$

with the nonlinearity arising in the dependence of  $h$  on  $E_n$  (see the Supporting Information for details on the numerical implementation).

One challenge in developing more accurate solvent models is the fact that nonlinear response<sup>45</sup> generally requires a charging process<sup>7</sup>, i.e. the expression  $\Delta G^{solv,es} = \frac{1}{2} q^T \varphi^{REAC} = \frac{1}{2} q^T L q$  no longer holds ( $L$  denotes the reaction-potential operator<sup>1,38</sup>). However, our previous work showed the remarkable fact that the solute reaction potential is *piecewise* linear, with the breakpoint at  $q = 0$ <sup>17</sup>, so that  $\varphi^{REAC} = L_+ q$  for  $q > 0$  and  $\varphi^{REAC} = L_- q$  for  $q < 0$ , with  $L_+ \neq L_-$ . The proposed NLBC in Eqs. 5 and 7 immediately explains this curious phenomenon: consider the limit  $\beta \rightarrow \infty$ , so that  $\tanh$  is constant everywhere, but discontinuous at  $q = 0$ . The Debye charging process<sup>46</sup> scales all charges uniformly, i.e.  $\hat{\rho}(r; \lambda) = \lambda \rho(r)$ , so the Coulomb field  $\frac{\partial \varphi^{Coul}}{\partial n}$  has the same sign for all finite  $\lambda$ . The Coulomb-field approximation (CFA) shows that the reaction field is nearly proportional to the direct Coulomb field, but slightly smaller in magnitude<sup>38,47,48</sup>, so for finite  $\lambda$ , at almost all  $\mathbf{r}_\Gamma$ , the total field  $E_n(\mathbf{r}_\Gamma; \lambda)$  has the same sign as  $E_n(\mathbf{r}_\Gamma; \lambda = 1)$ . This implies that almost everywhere on the surface, the  $\tanh$  boundary condition takes its limiting ( $\lambda \rightarrow 1$ ) value for any finite  $\lambda$ , which means that the boundary condition is essentially linear:  $(1 + g(r))\sigma(r) = \frac{\partial \hat{\varphi}_2}{\partial n} - \frac{\partial \hat{\varphi}_1}{\partial n}$ . With this justification, in this work we compute solvation free energies as  $\Delta G^{solv,es} = \frac{1}{2} q^T \varphi^{REAC}$ . Note that a more precise definition of the charging free energy would be piecewise *affine*, because the charging free energy also includes a linear term that results from the liquid-vapor interface potential<sup>17,49,50</sup>; as noted above, however, in the present work its influence is approximated via the offset parameter  $\gamma$ .

### III. RESULTS AND DISCUSSION

We parameterized the NLBC model using the Mobley et al. MD free-energy calculations, who studied asymmetry using fictitious bracelet and rod molecules<sup>30</sup> constructed from AMBER  $C_\alpha$  atoms with  $R_{\min}/2 = 1.908 \text{ \AA}$ . We obtained optimal results with  $\alpha = 0.5$ ,  $\beta = -60$ ,  $\gamma = -0.5$ , and a continuum-model  $C_\alpha$  radius of  $1.75 \text{ \AA}$  (a scale factor of approximately 0.92). Note that in this first exploration of the NLBC, we have parameterized against the overall solvation free energies computed by Mobley et al. rather than the more correct charging free energy.

Problem	Solvation errors		Asymmetry errors	
	RMSE	Max.	RMS	Max.
Rods	5.57	9.63	0.88	1.49
Bracelets (opposing)	2.88	6.10	2.04	3.08
Bracelets (distributed)	2.20	2.72	0.29	0.59
Bracelets (dipole)	2.67	3.52	0.85	1.09

TABLE I. Comparison of NLBC model to MD free-energy calculations of Mobley et al.<sup>30</sup> for rod and bracelet molecule test set. All energies are in kcal/mol. See Supporting Information for detailed results.

Figure 1 plots NLBC and MD free-energy calculations for ion charging free energies; the MD charging simulations used in our previous work<sup>17</sup> (see Supporting Information) and CHARMM Lennard-Jones parameters. We remind the reader that no additional parameters were fit in obtaining these NLBC results, i.e. ion radii were assigned  $R_{\text{ion}} = 0.92 R_{\min}/2$ . For additional data, ions were charged to both  $+1e$  and  $-1e$ , regardless of the charge on the real ion, and the NLBC accurately predicts these charging free energies as well. The largest deviations occur for radii less than  $1.4 \text{ \AA}$ , where discrete packing effects and actual dielectric saturation are likely.

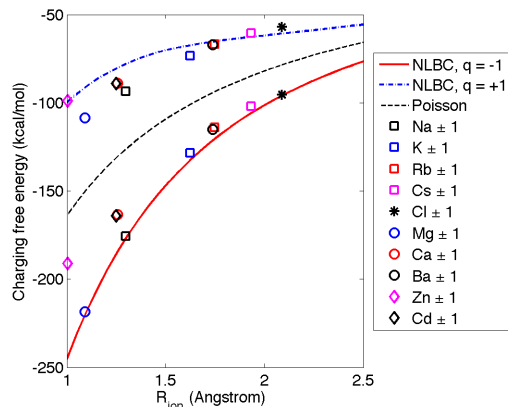


FIG. 1. Asymmetric polarization free energies for a monovalent central charge in a sphere, as a function of sphere radius. The labeled symbols denote results from MD free-energy calculations charging CHARMM monatomic ions from zero to  $+1e$  or  $-1e$ , with  $R_{\text{ion}} = 0.92 R_{\min}/2$ . The dashed black curve in the middle is the (charge-sign symmetric) Born polarization free energy.

Calculations for the Mobley test set are summarized in Table I; SI Figures 1–8 plot the NLBC and Mobley MD solvation free energies and asymmetry energies, and include illustrations of the test problems. The rod molecules are composed of 5 or 6 atoms along a line, with one atom possessing  $+1e$  charge, one with  $-1e$ , and the rest neutral. The asymmetry errors in Table I represent the difference in solvation energies when reversing the charged atoms' signs. The bracelet molecules are regular polygons with between 3 and 8 sides; atoms

are at the vertices (1.4 Å apart). Bracelets were simulated with three charge distributions: the “opposing” case had a  $+1e$  charge neutralized by two  $-0.5e$  charges positioned symmetrically on the opposite side. The “distributed” case has one  $+1e$  charge and a neutralizing  $-1e$  distributed equally on all the other atoms; the “dipole” case is similar to “opposing” but fixes the dipole moment<sup>30</sup>. Solvent charge-densities from the MD calculations<sup>30</sup> suggest that solvent packing may be responsible for size-dependent deviations; parameterizing radii for actual atoms should significantly reduce these errors.

To test the model on real but nonspherical molecules, we compared NLBC and MD charging free energies for isolated titratable amino acids in both protonated and unprotonated states (See Supporting Information for details on structure preparation). Parameters were from the CHARMM force field<sup>51</sup> when available, with other protonation states defined so that the protonated and unprotonated states had the same number of atoms. The MD free-energy-perturbation (FEP) calculations used the same protocol as the ions<sup>17</sup>, holding the solute rigid so that  $\epsilon_1 = 1$  unambiguously<sup>1</sup>. The deviations between our MD results and the MD calculations of Nina et al.<sup>52</sup> are small compared to the energies of interest, and likely due to our use of (i) periodic boundary conditions, (ii) a larger solvent box (1959 waters vs. 150), and (iii) slightly different backbone angles.

As in the ion and Mobley examples, the NLBC radii were defined by the scaling  $R = 0.92R_{\min}/2$ . The results in Figure 2 illustrate that the NLBC model correctly captures solvation free energies in both charge states, despite the fact that radii were not adjusted individually or even for the atomic charges. In contrast, standard Poisson model results computed using the Nina et al.<sup>52</sup> or PARSE<sup>53</sup> radii exhibit larger deviations, particularly for arginine, aspartic acid, cysteine, glutamic acid, and tyrosine. These data suggest that the differences between symmetric and asymmetric electrostatic models are robust with respect to radii (the PARSE calculations are merely suggestive because these calculations used the CHARMM charges; for consistent comparison to experiment, one should use PARSE charges with PARSE radii).

#### IV. CONCLUSION

We have proposed a Poisson-based theory that models charge-sign-dependent asymmetries in electrostatic solvation free energies using a nonlinear boundary condition (NLBC), while still using linear continuum theory in the solute and solvent volumes. The NLBC model accurately reproduces MD free-energy results for monatomic ions, the Mobley et al. bracelet and rod problems, and titratable residues, even though we have used charge-independent radii that were fixed by a single scaling factor applied to MD radii. Furthermore, the NLBC reduces smoothly to the standard Poisson model as the param-

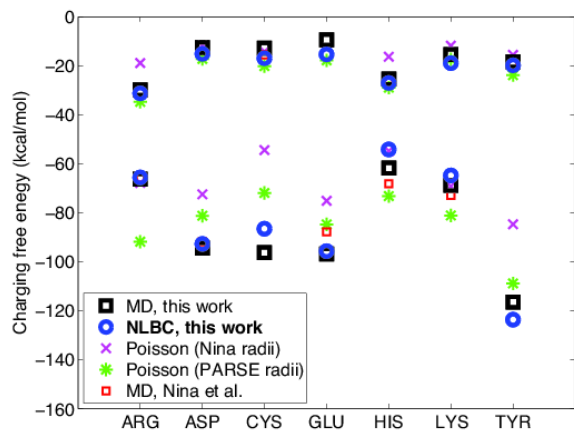


FIG. 2. Comparison of NLBC model to explicit-solvent MD FEP calculations for titratable residues with neutral blocking groups. MD results from Nina et al.<sup>52</sup> are shown where available; standard continuum model results are shown for Nina et al. radii and PARSE<sup>53</sup> (using CHARMM charges).

eter  $\alpha$  approaches zero. Finally, our boundary-element method implementation for non-trivial molecules demonstrates that the new model is easily implemented in numerical Poisson and Poisson-Boltzmann solvers.

Our introduction of a modified boundary condition to account for solvation-shell response follows a long history in continuum mechanics, where phenomenological techniques find applications in many areas of science and engineering to capture a particular physical behavior in continuum theory rather than modeling or deriving it from first principles<sup>54–56</sup>. Non-equilibrium micro-scale gas flows offer a well-developed example: velocity-slip and temperature-jump boundary conditions are simplified phenomenological approaches to represent both non-equilibrium and gas-surface interaction effects occurring near solid walls. Such boundary conditions were first suggested in the 19th century by Maxwell<sup>57</sup> and von Smoluchowski<sup>58</sup>, respectively. More recent examples include the partitioning of minerals at phase boundaries in geophysics<sup>59</sup>, tumor growth<sup>60</sup>, the deformation of biological membranes<sup>61</sup>, and thin electric double layers in electro-osmotic flow<sup>62</sup>.

Much as Beglov and Roux showed that solvent response approaches the linear Poisson model in the limit as the solvent molecule approaches zero size<sup>63</sup>, our model emphasizes that the nonlinear response is generally localized in the first solvent shell. Conceptually, the nonlinear boundary condition penalizes negative surface charge because the larger water oxygen cannot approach a solute charge as closely as the water hydrogens can. From a boundary-integral point of view, this has the same effect as adjusting the atomic radii, an approach pioneered by Latimer et al.<sup>5</sup>, and extended recently to GB models<sup>16,24,31,32</sup>. Purisima’s work is particularly relevant due to their use of surface-charge boundary-integral approach, adjusting GB radii using  $\sigma(\mathbf{r})$ <sup>24,31</sup>. Our work dif-

fers substantially from these approaches because we have included asymmetry directly in the underlying Poisson model.

The present theory can be extended in several important ways. First, the proposed NLBC model has only three parameters whose particular dependencies on solvent model have not yet been established theoretically. Second, it seems straightforward to include ionic screening via the Poisson–Boltzmann equation. Third, the proposed NLBC depends exclusively on the normal electric field; improved models might include local curvature or higher-order moments of the potential. Importantly, the latter could distinguish between small-magnitude charges near the surface, and larger charges further away<sup>16</sup>. Fourth, water’s length-scale-dependent dielectric behavior might be included using nonlocal electrostatics<sup>7,20,64–66</sup>. The new model also does not necessarily capture specific hydrogen-bonding effects like AGBNP2 does<sup>2</sup>, which motivates future work comparing the two approaches.

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## SUPPORTING INFORMATION

Figures comparing NLBC and MD calculations for the Mobley test set<sup>30</sup>. The source code (MATLAB) and surface discretizations for running the nonlinear boundary-condition calculations, data files, parameters, and scripts for preparing and running the MD calculations of titratable residues, as well as source code to generate the figures, are freely and publicly available online at <https://bitbucket.org/jbardhan/si-nlbc>.

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